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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/689,366	10/12/2000	Mike Rothe	T95-005-2	7997

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EXAMINER	
LEFFERS JR, GERALD G	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 01/15/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/689,366	ROTHE ET AL.	
	Examiner	Art Unit	
	Gerald Leffers	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-16* is/are pending in the application.

4a) Of the above claim(s) *11 and 14-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,12 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Receipt is acknowledged of applicants' preliminary amendment, filed 10-12-00 as Paper No. 3, in which claims 1-9 were cancelled and in which new claims 10-16 were added.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 10, 12, 13, drawn to an isolated human cellular inhibitor of apoptosis protein (c-IAP1), and derivative thereof, classified in class 530, subclass 350.

II. Claims 11-12, drawn to an isolated human cellular inhibitor of apoptosis protein (c-IAP2), classified in class 530, subclass 350.

III. Claims 14-15, drawn to a binding assay comprising c-IAP1, c-IAP2 or derivatives thereof, classified in class 435, subclass 7.1.

IV. Claim 16, drawn to an in vitro method of inhibiting TNF-mediated apoptosis comprising administering c-IAP to a target cell, classified in class 435, subclass 375.

The inventions are distinct, each from the other because of the following reasons:

The proteins of Group I and the proteins of Group II are chemically, biologically, structurally and functionally distinct from each other and, thus, one group does not render the other obvious. The different proteins of the two groups comprise distinct functional domains that dictate the functional capabilities of the apoptosis inhibitors found within the two groups

(e.g. different targets for inhibition). Therefore, the inventions of the two groups are capable of supporting separate patent.

Inventions of Groups I-II and Groups III-IV are related as products and processes of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the products of Groups I and II can be used in the patentably distinct methods of Groups III and IV.

The inventions of Groups III and IV are biologically and functionally different and distinct from each other, and thus one does not render the other obvious. The methods of Groups III and IV comprise steps which are not required for, or present, in the methods of the other Group: incubating a mixture of a candidate modulator of c-IAP with c-IAP and a natural intracellular human c-IAP binding target (Group III) and introduction of a composition comprising a c-IAP protein into a target cell (Group IV). The end results of the methods are different: identification of a compound that modulates c-IAP interaction with a target receptor (Group III) and inhibition of TNF-mediated apoptosis in a cell in vitro (Group IV).

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification (Groups I-II and Groups III-IV), restriction for examination purposes as indicated is proper. For Groups I-II there is a different sequence search required for the different and distinct polypeptides of the two groups. Therefore, restriction between Groups I and II is deemed proper.

During a telephone conversation with Richard Osman on 1-3-02 a provisional election was made with traverse to prosecute the invention of Group I, claims 10, 12 and 13. Affirmation of this election must be made by applicant in replying to this Office action. Claims 11, 14-16 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10 and 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims are directed towards an isolated human cellular inhibitor of apoptosis protein (c-IAP) comprising specific domains derived from the two c-IAP proteins of the invention. Claim 10 appears to be directed toward the 3rd BIR domain of c-IAP1 (amino acids

287-334 of SEQ ID NO: 2). Claim 12 appears to be directed towards hybrid proteins comprising at least 2 BIR domains derived from c-IAP1 or c-IAP2. The rejected claims encompass embodiments where the human c-IAP protein comprises other functional domains in addition to the BIR and RING finger domains described in the art or in the instant specification.

The specification describes the isolation of cDNAs encoding c-IAP1 and c-IAP2 by probing human cDNA libraries with a nucleic acid encoding a murine version of c-IAP. The human c-IAP proteins are described as having significant similarity to the mouse version of c-IAP (84% and 72%, respectively, for c-IAP1 and c-IAP2) and 73% homology to one another. Unlike the insect viral analogs, the mammalian IAPs (c-IAP1 and c-IAP2) are described as comprising 3 BIR domains rather than two such domains. However, unlike NAIP, another mammalian apoptosis inhibitor, the instant proteins comprise a RING finger motif similar to ones found in the insect viral analogs. Yeast two-hybrid analysis results are described which indicate that c-IAP1 and c-IAP2 interact with TRAF1 and TRAF2, two intracellular receptors for TNF. Deletion and hybrid experiments indicate that the BIR domains of c-IAP1 and c-IAP2 represent novel protein::protein interaction domains. The N-terminal domain of c-IAP1, comprising the 3 BIR motifs, is described as being sufficient to mediate interaction with the two receptors. The RING finger domain does not appear to be essential for c-IAP interaction with the TRAF receptors.

It is clear from the description provided by the specification that c-IAP1 and c-IAP2 share several similar structural/functional domains with one another and with different apoptosis inhibitors known in the art. For example, it is noted that the first BIR domains from each of c-IAP1 and c-IAP2 (described by SEQ ID NOS: 1 and 2) differ at only 1 amino acid residue out of

a total of 55 residues. However, it is also evident from reading the specification that there are significant differences between the previously known inhibitors of apoptosis and c-IAP1/c-IAP2, as well as between c-IAP1 and c-IAP2 (e.g. 27% non-homology between the two proteins). There is no structural/functional framework provided in the specification to allow one of skill in the art to envision exactly what a 3rd c-IAP protein obtained from humans would look like. For example, would such a third c-IAP protein necessarily comprise a RING-finger domain? Would a 3rd c-IAP protein comprising SEQ ID NO: 5 or SEQ ID NO: 6 necessarily comprise other BIR domains similar to the ones described herein (e.g. SEQ ID NOS: 7-10)? The specification teaches that it is the BIR domains that are likely to provide target specificity for c-IAP/target interaction. If additional human c-IAP proteins exist, it seems likely that they could be directed to other protein targets involved in mediating apoptosis. What would the BIR domains of such a protein look like? Again, the specification provides no basis to envision the primary amino acid sequence/structure of such a human c-IAP protein.

The prior art teaches that it is difficult to predict the structural/functional properties of a protein having a given primary amino acid sequence because the relationship between the sequence of a protein and its tertiary structure (in essence the structure which defines its activity), is not well understood and is not predictable as evidenced by Berendsen (Science. 1998, Vol. 282, pages 642-643; see the entire document). This reference teaches that "Thus, one of the "grand challenges" of high-performance computer-predicting the structure of proteins-acquires much of the flavor of the Holy Grail quest of the legendary knights of King Arthur: It is extremely desirable to possess but extremely elusive to obtain." (Page 643, columns 1-2). The whole reference teaches about the unpredictability in the art concerning protein structure, and

failures to make it predictable. Thus, as taught by Berendsen, the state of the art with regard to predicting the structural/functional characteristics of a protein having a given amino acid sequence is underdeveloped. Therefore, the prior art does not provide a structural/functional basis for one of skill in the art to envision additional embodiments of the claimed human c-IAP proteins comprising one or more of the recited domains of c-IAP1 and c-IAP2.

Given that the rejected claims encompass proteins comprising, or lacking, additional functional elements (e.g. BIR and RING-finger domains) to those described in the specification, and given that there is no structural/functional framework provided in the specification or prior art to envision additional embodiments of the claimed invention other than c-IAP1 and c-IAP2, one of skill in the art would not have been able to envision a representative number of embodiments of the claimed c-IAP proteins to describe the genus of such proteins. Therefore, one of skill in the art would have reasonably concluded applicants were not in possession of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 is vague and indefinite in that the metes and bounds of the phrase "comprising at least two of" are unclear. It is unclear whether the phrase refers to different combinations of the 3 different BIR domains, combinations of the same BIR domain (e.g. two copies of SEQ ID

NO: 5 together on a polypeptide), or both. It would be remedial to amend the claim language to clearly indicate which combinations of sequences fall under the limitation of "at least two of".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim 12 is rejected under 35 U.S.C. 102(e) as being anticipated by Korneluk et al (U.S. Patent No. 5,919,912; see the entire document).

The '912 patent teaches the isolation of nucleic acid sequences encoding mammalian IAP polypeptides, methods of producing IAP polypeptides from such sequences, methods of using such nucleic acids and polypeptides to inhibit apoptosis in cells, and methods for identifying modulators of human IAP proteins (e.g. Abstract). One of the IAP polypeptides disclosed in the '912 patent (SEQ ID NO: 8) is ~99% identical to the amino acid sequence of c-IAP1 (SEQ ID NO: 2) disclosed by the instant application. This human IAP protein comprises first and second

domains identical to SEQ ID NO: 5 and SEQ ID NO: 7, respectively (see the attached search reports). Thus, the issued patent teaches an isolated human cellular inhibitor of apoptosis protein comprising at least two of the recited domains.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

ggl
January 13, 2002

DAVID GUZO
PRIMARY EXAMINER